CLINICAL STUDY

Lack of cross-reactive allergic response to brimonidine in patients with known apraclonidine allergy

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Abstract

Purpose **To assess the allergenic potential of topical brimonidine 0.2% in patients shown to be allergic to apraclonidine 0.5%.**
Methods **Eighteen glaucoma patients who developed allergy to apraclonidine were enrolled. Allergy was graded and documented photographically. Apraclonidine was then discontinued until the allergy resolved. Grading and photography were repeated, following which treatment with brimonidine was initiated. Patients were examined 1 h after the initial drop of brimonidine, twice weekly for 6 weeks, and at 3 monthly intervals thereafter. All other anti-glaucoma medications were continued.**
Results **Mean patient age was 66.3 ± 14.9 years (range 33.5–89.3 years). The mean time to apraclonidine allergy from initial exposure was 12.9 ± 12.9 months (range 2.1–46.8 months). For the 10 patients rechallenged with apraclonidine, the mean time to allergy was 13.6 ± 10.2 days (range 3–32 days). Mean duration of brimonidine therapy was 140.7 ± 66.2 days (range 14–286 days), with 11 patients reaching at least 150 days of follow-up. Two patients developed symptomatic brimonidine allergy at 138 and 201 days respectively. For those patients who did not develop symptoms of allergy to brimonidine, there was no significant change in any of the parameters by which allergy was graded throughout the study.**
Conclusions **Patients with known apraclonidine allergy do not develop an early allergic response to brimonidine. These data rule against a cross-reactive allergic response between these two alpha$_2$-adrenoreceptor agonists.**

Key words Allergy, Alpha-agonist, Apraclonidine, Brimonidine

In 1966, Makabe[1] demonstrated that clonidine, a relatively selective alpha$_2$-agonist, lowered intraocular pressure (IOP) after intravenous administration in humans. Hasslinger[2] demonstrated the same effect after topical application. However, it was associated with a marked lowering of systemic blood pressure.[3,4] Apraclonidine hydrochloride 0.5% (Iopidine, Alcon Laboratories, Fort Worth, TX), the first relatively selective alpha$_2$-agonist approved for ocular use in the United States, is an imidazoline derivative of clonidine with an additional amine group on the para-position of the benzene ring. This increases its polarity relative to clonidine and decreases its corneal penetration coefficient and ability to cross the blood–brain barrier.[5] Apraclonidine has fewer centrally mediated cardiovascular side effects than clonidine.[6–9] However, allergic reactions occur in 19–36% of patients using apraclonidine 0.5% twice daily[10] and in up to 48% of patients using the 1% concentration.[11]

Brimonidine tartrate 0.2% (Alphagan, Allergan, Irvine, CA) is a new, relatively selective alpha$_2$-agonist recently approved for lowering IOP. It has a quinoxaline ring system and bromine as a side group instead of chlorine, is more polar (less lipophilic) than clonidine, and appears to be a more oxidatively stable compound.[12] The reported rate of ocular allergy to brimonidine is 4.8–9.6%.[13,14] The purpose of this study was to determine whether glaucoma patients with known apraclonidine allergy would develop an allergic response upon institution of brimonidine treatment.

Methods

This study was approved by the institutional review board of the New York Eye and Ear Infirmary. After informed consent was obtained, 18 glaucoma patients (10 men, 8 women) with known apraclonidine allergy were enrolled. Ten patients had a history of apraclonidine allergy and agreed to be rechallenged in order to document the allergy. The other 8 patients presented with apraclonidine allergy characterised by ocular itch, conjunctival hyperaemia and a follicular reaction. Apraclonidine allergy was

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Table 1. *Days to apraclonidine allergy on rechallenge (if performed) and duration of brimonidine therapy*

Patient no.	APC rechallenge	Time to allergy after APC rechallenge (days)	Duration of Br treatment (days)	Br allergy
1	N	N/A	57	N
2	Y	3	188	N
3	Y	32	286	N
4	Y	21	147	N
5	Y	6	41	N
6	Y	3	201	Y
7	Y	14	212	N
8	Y	7	213	N
9	N	N/A	146	N
10	N	N/A	138	Y
11	N	N/A	167	N
12	N	N/A	161	N
13	N	N/A	14	N
14	Y	26	122	N
15	Y	3	113	N
16	N	N/A	64	N
17	N	N/A	139	N
18	Y	21	119	N

APC, apraclonidine; Br, brimonidine; Y, yes; N, no; N/A, not applicable.

documented in all subjects with slit lamp photography. Conjunctival follicles, papillae, erythema and oedema were graded on a scale of 0 (absent) to 3 (severe) by one observer. Apraclonidine was then discontinued until the allergy resolved.

Grading and photography were repeated, following which brimonidine treatment was initiated. Patients were examined 1 h after instillation of the initial drop of brimonidine, and then twice weekly for 6 weeks, at 3 months, and then at 3 monthly intervals. At each visit, patients were questioned about symptoms of ocular redness, discomfort and itching, and were instructed to return for examination immediately if these symptoms of allergy developed between study visits. Photography was repeated at the 6 month visit or when an allergic response occurred.

All subjects used apraclonidine or brimonidine in conjunction with other anti-glaucoma medications. The number and dosage of these other anti-glaucoma medications were not altered during the study period.

Results

Mean patient age was 66.3 ± 14.9 years (range 33.5–89.3 years). For 4 patients with a history of apraclonidine allergy, medical records were not available to determine the time from initial exposure to the development of the allergic response. For the remaining 14, the mean time to diagnosis of allergy from initial exposure was 12.9 ± 12.9 months (range 2.1–46.8 months). For the 10 patients rechallenged with apraclonidine, the mean time to allergy was 13.6 ± 10.2 days (range 3–32 days). For the 8 patients newly presenting with apraclonidine allergy, the signs of allergic response remitted in all cases after washout and prior to institution of brimonidine therapy, indicating apraclonidine to have been responsible for the allergic response. The mean time for apraclonidine washout and allergy resolution was 19.9 ± 11.7 days (range 8–56 days).

Mean duration of brimonidine therapy was 140.7 ± 66.2 days (range 14–286 days), with 11 patients reaching at least 150 days of follow-up. Two patients developed symptomatic brimonidine allergy at 138 and 201 days respectively. They reported no difference in the degree of itching and redness between apraclonidine and brimonidine allergies. In both these patients, signs of allergy remitted soon after discontinuation of brimonidine. Five patients discontinued brimonidine therapy for reasons other than allergy (1 patient moved away and 4 others underwent trabeculectomy). A summary of apraclonidine rechallenge and duration of brimonidine therapy is provided in Table 1.

The change in allergy grading parameters at each study interval is outlined in Table 2. From apraclonidine allergy to washout there was a decrease in conjunctival follicles ($p<0.001$, chi-squared), papillae ($p = 0.002$),

Table 2. *Change in allergy grading parameters in subjects without symptomatic brimonidine allergy*

	APC allergy ($n = 16$)	Washout ($n = 16$)	Week 6 ($n = 15$)	Week 12 ($n = 12$)	Month 6 ($n = 11$)
Follicle grade	2.12 + 0.85	0.06 + 0.25	0.07 + 0.26	0.08 + 0.29	0.18 + 0.66
Papillae grade	1.75 + 0.62	0.69 + 0.25	0.33 + 0.49	0.45 + 0.78	0.40 + 0.66
Erythema grade	1.56 + 0.73	0.50 + 0.63	0.53 + 0.64	0.54 + 0.66	0.36 + 0.50
Oedema grade	0.44 + 0.63	0.06 + 0.25	0.06 + 0.26	0.17 + 0.39	0.09 + 0.30

All parameters improved from the time of apraclonidine allergy to washout, while there were no significant differences in any parameter throughout the 6 months of brimonidine therapy.

erythema (p = 0.003) and oedema (p = 0.070). There was no significant change in any of these parameters from the completion of the washout period to study endpoint.

Comment

The mean time from initial apraclonidine exposure to diagnosis of allergy in this study was 12.9 ± 12.9 months – longer than in previous studies. Arujo *et al.*[15] reported allergy presenting as late as 35 weeks, but Nagasubramanian *et al.*[11] reported all allergic reactions occurring within 60 days. However, we have seen allergies develop as late as 2 years after initiating treatment with apraclonidine.[16] The fact that we evaluated the onset of allergy retrospectively might increase the reported time to the development of allergy, as early stages with a minimum of complaints may not have been documented. Data were not available for 4 patients with a history of apraclonidine allergy, so their time from initial apraclonidine exposure to allergy diagnosis could not be included. Also, several patients presented having had symptoms of chronic redness and itching for some time and had findings of apraclonidine allergy on initial examination. All 10 patients rechallenged with apraclonidine presented within 33 days with a follicular conjunctivitis that resolved after discontinuation of the drug.

If the allergic response to brimonidine was cross-reactive rather than primary, we would expect it to have occurred within 6 weeks of initiation of brimonidine therapy, since patients rechallenged with apraclonidine all presented within 4 weeks. However, the first allergic response to brimonidine occurred at greater than 12 weeks. Therefore, the allergic responses to brimonidine we observed most likely represented initial allergic reactions. Despite the small sample size, the rate of brimonidine allergy in this study (2/18, 11.1%) agrees with previously published reports and suggests that the rate of brimonidine allergy is not increased in patients who have a history of apraclonidine allergy. Furthermore, those patients who had no symptoms of allergy did not develop subtle signs of allergy (e.g. an increase in follicle grade) during the study period.

These data raise some interesting questions regarding the nature of alpha-agonist-induced ocular allergy in general, and the difference between apraclonidine and brimonidine in particular. What accounts for toxic follicular conjunctivitis associated with topical alpha-agonists? The preservative, benzalkonium chloride, can also cause an allergic response.[17] However, this preservative is present in both apraclonidine (0.01%) and brimonidine (0.005%), ruling it out as a cause of the allergic reactions. Other, inactive ingredients are also present. This vehicle is similar to other ophthalmic medications which have not been reported to cause follicular conjunctivitis. Therefore, the alpha-agonist itself seems the most likely component to have a role in the allergic reaction.[18] Recent studies on drug hypersensitivity reactions suggest that most topical drugs are not immunogenic *per se*, but their metabolites become immunogenic through interactions with cellular macromolecules to produce haptens which can sensitise T-cells.[19,20] Even after rechallenge, metabolites must react with local cellular proteins before sensitised T cells can respond. This may explain why in this study allergy on rechallenge with apraclonidine occurred at up to 33 days compared with a classic type IV hypersensitivity reaction where a response to rechallenge typically occurs within 72 h.

Why are apraclonidine and brimonidine not cross-reactive, and why do they have different allergy rates? Basketter *et al.*[19] pointed out that true cross-allergy may have several components. The metabolites of sensitising and triggering agents probably require structural similarity to induce a cross-allergy. Apraclonidine and brimonidine have different chemical reactivities[21] and thus produce different metabolites. Apraclonidine, like adrenaline, possesses a hydroquinone-like subunit which is oxidatively labile. The oxidative potential of apraclonidine is similar to that of amodiaquine, which is a known allergen.[22] Oxidatively labile quinones are associated with greater reactivity with thiol groups to produce adducts that can cause allergic or cytotoxic reactions.[23] Brimonidine, like clonidine, lacks a hydroquinone subunit and therefore is oxidatively stable. Brimonidine does not form thiol adducts as readily as apraclonidine. The different oxidative potentials of apraclonidine and brimonidine may help to explain their lack of cross-reactivity and the lower allergy rate of brimonidine compared with apraclonidine.

In summary, there was no immediate cross-reactive allergic response to brimonidine in these patients with known apraclonidine allergy. This lack of cross-reactivity to brimonidine may be due to the different chemical reactivities of apraclonidine and brimonidine. Patients with known apraclonidine allergy can be treated with brimonidine with little risk of an immediate allergic response.

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